MICROBIOLOGY

Simple Hosts May Help Reveal How Bacteria Infect Cells

Easily studied organisms such as fruit flies, worms, and yeast are turning out to be good hosts for bacteria that cause human diseases

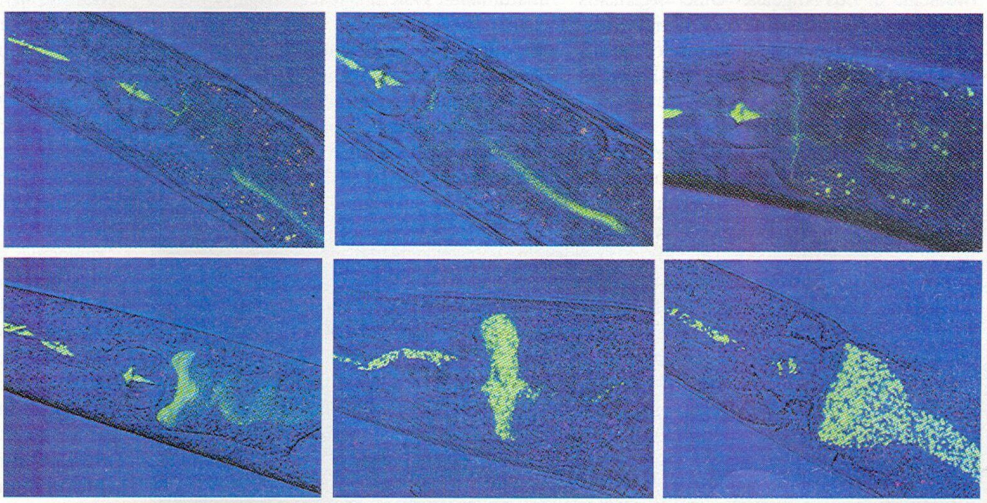
When microbiologist Laurence Rahme began speculating in the early 1990s that some human pathogens might infect plants, "a lot of people looked at me in a very weird way," she recalls. And when she suggested that the infected plants might respond—at least on a molecular level—in ways that mimic those of sick people, "people told me I was crazy." After all, plants don't cough or throw up. Given the physiological gulf between plants and people, the whole notion seemed far-fetched.

But Rahme persevered, encouraged by her thesis adviser, Nickolas Panopoulos of the University of California, Berkeley, and a later mentor, geneticist Frederick Ausubel of Harvard Medical School in Boston. Today, she is at the vanguard of a new area of microbiological research: using not only plants but also other simple organisms—such as the roundworm *Caenorhabditis elegans*, the social amoeba *Dictyostelium discoideum* (sometimes referred to as slime mold), the fruit fly, and even yeast—to study the interactions between harmful bacteria and their hosts.

One indication of the field's newfound respectability came at this year's meeting of the American Society for Microbiology (ASM),* which held its first-ever session on the topic. "I can't tell you how many people have told me how they're going to test worms with their [infection] model," says Colin Manoil, a geneticist at the University of Washington, Seattle. "This field is in its infancy, but it's going to become huge."

Driving this work are findings that support Rahme's initial speculation: Important human pathogens—including *Pseudomonas aeruginosa*, a common cause of infections in burn victims and cystic fibrosis patients, and *Legionella pneumophila*, which causes Legionnaire's disease—invade and harm simple organisms. What's more, these infections require many of the same bacterial genes needed to make mammals sick. These observations suggest that even though simple organisms aren't perfect models for complex hosts—in particular, they lack the highly specific immune responses that mammals deploy when fighting off microbes—the basic mechanisms by which bacteria establish infections in the various organisms may be similar.

And that, in turn, suggests that the unconventional hosts may help researchers explore what microbiologist Samuel Miller, who's also at the University of Washington, Seattle, calls "the real big frontier"—the mammalian side of bacterial invasions. Identifying the host proteins that either promote infections or help ward them off would not only shed light on the basic mechanisms of infectious diseases but also provide potential new targets for antibacterial drugs.



Model infection. When *C. elegans* worms feed on *S. typhimurium*, the bacteria proliferate in the animals' intestines, causing marked distention (bottom panels). That does not happen in worms feeding on nonpathogenic *E. coli* bacteria (top panels).

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Promising parallels, powerful genetics

Progress in identifying those host proteins has been slow, mainly because the standard models for human diseases—usually mice or mammalian cells in culture—are so genetically unwieldy that they don't readily lend themselves to the experimental analyses needed to do the job. But such studies are relatively easy to carry out with genetically tractable animals such as yeast, worms, and fruit flies.

Indeed, scientists have appreciated the power of those organisms for decades. So it might seem surprising that only now are significant numbers of laboratories using them to study pathogenesis. "It's one of those things where once it starts happening, you wonder why it didn't happen before," says Manoil. As Rahme found when she made her original proposals, however, many investigators simply weren't convinced that the approach would work. "I don't think people realized that there would be so many conserved features of pathogenesis," says Ausubel. But Rahme says that when she shared her thoughts with the Harvard geneticist before joining his lab as a postdoc in 1992, she found him unusually open minded. "I thought it was a long shot, but a great idea," says Ausubel.

Rahme's Berkeley adviser, Panopoulos, had told her about several little-known discoveries made 15 to 20 years earlier, suggesting that some strains of *P. aeruginosa* cause illness in both plants and humans. Those experiments had been performed on celery, lettuce, and potato plants, but Rahme wanted to study a plant with a genetic makeup that was better understood and more easily manipulated. So, she sifted through a collection of 75 *P. aeruginosa* strains, looking for any that would sicken the well-studied plant, *Arabidopsis thaliana*.

By 1995, Rahme had found two bacterial strains that fit the bill—they rotted *A. thaliana* leaves—and she decided to focus on the one that had originally been isolated from a burn patient. She found that mutants that did not produce proteins known to be important for virulence in

* 21–25 May in Los Angeles, California.